PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 16230

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

9 NOV 2005

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/018921	07.06.2004	09.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/22

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA.

European Patent Office
D-80298 Munich
Tel +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Voigt-Ritzer, H

Telephone No +49 89 2399-7187

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/018921

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/018921

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-32 partially

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	15-17, 28, 29, 32
	No:	Claims	1-14, 18-27, 30, 31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	15-17, 28, 29, 32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2004/018921

Reference is made to the following documents:

D2: SHAH M ET AL: "NEUTRALISATION OF TGF-BETA1 AND TGF-BETA2 OR EXOGENOUS ADDITION OF TGF-BETA3 TO CUTANEOUS RAT WOUNDS REDUCES SCARRING" JOURNAL OF CELL SCIENCE, CAMBRIDGE UNIVERSITY PRESS, LONDON, GB, vol. 108, no. PART 3, 1 March 1995 (1995-03-01), pages 985-1002

D3: Monoclonal anti-TGF-b1 antibody. R and D Systems, Ordering Information, Catalog Number: MAB2401, 29.1.2003

D4: LUCAS C ET AL: "THE AUTOCRINE PRODUCTION OF TRANSFORMING GROWTH FACTOR-BETA1 DURING LUMPHOCYTE ACTIVATION A STUDY WITH A MONOCLONAL ANTIBODY-BASED ELISA" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 145, 1 September 1990 (1990-09-01), pages 1415-1422

D6: FLANDERS K C ET AL: "ANTIBODIES TO PEPTIDE DETERMINANTS IN TRANSFORMING GROWTH FACTOR BETA AND THEIR APPLICATIONS" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 27, 1988, pages 739-746

D7: ELLINGSWORTH L R ET AL: "TRANSFORMING GROWTH FACTOR-BETAS ARE EQUIPOTENT GROWTH INHIBITORS OF INTERLEUKIN-1-INDUCED THYMOCYTE PROLIFERATION" CELLULAR IMMUNOLOGY, vol. 114, no. 1, 1988, pages 41-54

The present application pertains to TGF-b1 binding compositions which are based on the Fab fragment clone "1021". This clone has been isolated from an anti human TGF-b1 antibody library and is characterized by specific CDRs (heavy chain CDR1-3: Seq ID No: 13-15, light chain CDR1-3: Seq ID No: 22-25).

Re Item IV

Lack of unity of invention

As already mentioned in the reasoning for additional search fees the present application does not comply with the requirements of unity of invention. Only claims related to the first invention have been searched.

According to Rule 66.1 (e) claims for which no international search report has been established need not to be subject of international preliminary examination.

Consequently, only those parts of claims 1-32 which are referring to the TGF-beta1 binding composition "1021" and Seq ID No:13-15, 22-24 as well as Seq ID No: 2 and 4 are examined.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Antibodies which are specific for the isoform TGF-beta1 and which have the ability to neutralize TGF-beta1 are already known in the prior art. Even though in most of the documents the exact sequence encoding the CDRs is not disclosed this structural feature can be considered as being an inherent feature (see Guidelines C, IV, 7.5). Consequently is document D3 novelty destroying for the subject-matter of claims 1-3, 4ai-vi, 4bi,ii,x,xi, 5-13, 14n, 18-26 and 27l because it discloses a monoclonal anti-TGF-beta1 antibody MAB2401 which displays "negligible cross-reactivity with rhTGF-beta2 and rhTGF-beta3" and has an "ability to neutralize the bioactivity of human TGF-beta1" (Figure 2). The mouse antibody belongs to the IgG class and is reconstituted in sterile PBS.

Document D4 is novelty destroying for the subject-matter of claims 1-3, 4ai-vi, 4bi,ii,x,xi, 5-13, 14n, 18-26, 27l and 30-31 because it discloses the monoclonal mouse anti-rhTGF-beta1 antibody 4A11 which neutralizes and immunoprecipitates only rhTGF-beta1 (abstract). The mAb were purified and stored sterile (page 1416, 1. column, 3. paragraph). It was further used in an ELISA for detecting TGF-beta1 produced by human PHMCs (Figure 3).

The subject-matter of those parts of claims 1-14, 18-27 and 30-31 which are comprised in the 1. invention is not considered to be new in the light of the disclosure of documents D3 or D4.

There exist also documents in the prior art (D2, D6 and D7) which disclose polyklonal anti-TGF-beta1 antibodies. In view of the fact that the specific CDR sequences can be considered as inherent feature documents D2, D6 and D7 are novelty destroying for those parts of claims 1-13 and 30 which are comprised in the 1. invention. Documents D7 disclose a polyklonal anti-TGF-beta1 serum which can specifically neutralize the biological actions of TGF-beta1 and can compete with the TGF-beta1:receptor binding. These antibodies do "not neutralize the anti-proliferative action

of TGF-b2" (abstract) and can consequently be considered to be specific for the isoforme TGF-beta1.
Document D2 discloses TGF-beta1 "isotype specific neutralising antibodies" (abstract) that was raised in turkey against porcine TGF-beta1 (Table 1) and used to analyse the role of TGF-beta1 (as compared to TGF-beta2 or TGF-beta3) in wound healing.
Document D6 discloses an antiserum raised against TGF-beta1 which neutralizes the biological activity of TGF-beta1 and has "limited cross-reactivity with TGF-beta2" (abstract).

Those claims which are considered to be new, namely those parts of claims 15-17, 28, 29 and 32 which are involved in the 1. invention do not involve an inventive step for the following reasons.
The subject-matter of claims 15-17, 28 and 29 refers to the humanized form of the antibody which has been considered to be part of the prior art. Humanizing antibodies however belong to the routine work of immunologist and do not involve an inventive step.
The subject-matter of claim 32 refers to a kit comprising the binding-composition that has been considered to be not new. Putting a known composition together with instruction material and a compartment providing segregation of said composition in a kit is not considered to be inventive, either.